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ORIGINAL ARTICLE

Vitamin D and cognitive function

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Abstract

The role of vitamin D in skeletal health is well established, but more recent findings have also linked vitamin D deficiency to a range of non-skeletal conditions such as cardiovascular disease, cancer, stroke and metabolic disorders including diabetes. Cognitive impairment and dementia must now be added this list. Vitamin D receptors are widespread in brain tissue, and vitamin D's biologically active form [1,25$(OH)_2$D3] has shown neuroprotective effects including the clearance of amyloid plaques, a hallmark of Alzheimer's Disease. Associations have been noted between low 25-hydroxyvitamin D [25(OH)D] and Alzheimer's disease and dementia in both Europe and the US. Similarly, the risk of cognitive impairment was up to four times greater in the severely deficient elders (25(OH)D $<$ 25 nmol/L) in comparison with individuals with adequate levels ($\geq$ 75 nmol/L). Further studies have also shown associations between low 25(OH)D concentrations and cerebrovascular events such as large vessel infarcts, risk of cerebrovascular accident and fatal stroke. Cross-sectional studies cannot establish temporal relationships because cognitive decline and the onset of dementia itself may influence vitamin D concentrations through behavioural and dietary changes. However, two large prospective studies recently indicated that low vitamin D concentrations may increase the risk of cognitive decline. Large, well designed randomized controlled trials are now needed to determine whether vitamin D supplementation is effective at preventing or treating Alzheimer's disease and dementia.

Key Words: *Alzheimer's disease, dementia, cognition, cognitive decline, calcitriol*

Introduction

Vitamin D has long been known to be essential for skeletal health, but growing evidence also suggests an important role in non-skeletal age-related diseases such as cancer [1,2], cardiovascular disease [3], type 2 diabetes [4] and stroke [5]. Low concentrations of serum 25-hydroxy vitamin D [25(OH)D], a circulating biomarker for vitamin D status, are also associated with dementia [6,7]. The disease devastates families and requires substantial care, particularly in the later stages. The majority of people with dementia (currently around 36 million people worldwide [8]) suffer distressing neuropsychiatric symptoms progressing to total dependency and ultimately death [9]. Some drugs such as donepezil provide modest short term symptomatic improvements [10,11], but no treatment currently exists for prevention or disease modification. The development of a safe, cost-effective solution would clearly have an enormous global impact.

Vitamin D and the ageing brain

The hormonally active form of vitamin D, 1,25$(OH)_2$D3, produces biological effects in over 50 tissues [12]. An early study of Alzheimer's disease (AD) patients revealed the gene expression of vitamin D receptors in humans [13], and vitamin D receptors are widespread in both neurons and glial cells [14,15]. 1,25$(OH)_2$D3 strongly stimulates phagocytic clearance of amyloid β (Aβ) plaques, a hallmark pathological lesion in AD which triggers

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neurodegeneration in primary cortical neurons [16]. $1,25(OH)_2D3$ treatment protects against apoptosis in the macrophages of patients with AD [17] and glucocorticoid-induced apoptosis in hippocampal cells [18]. Vitamin D has direct antioxidant effects [19] and also upregulates the production of several neurotrophic factors which promote the survival, development and function of neurons [20,21]. Animal models propose that vitamin D may also increase endogenous neuroprotection against calcium toxicity [22,23], suggesting a link to the altered neuronal Ca^2+ homeostasis [24,25] which is associated with AD and cognitive impairment. Several studies also reveal associations between 25(OH)D deficiency and white matter abnormalities, large vessel infarcts [26], cerebrovascular accident [5] and fatal stroke in coronary angiography patients [27]. Low 25(OH)D concentrations may increase the risk of cerebrovascular pathology and mediate the risk of dementia via increased hypertension [28], diabetes [4]cardiovascular disease [29] and atherosclerosis [30].

Vitamin D concentrations and dementia

Several studies have reported associations between low a serum vitamin D concentration and all-cause dementia/AD compared to healthy controls [31,32]. For example in the US, participants with vitamin D deficiency (25(OH)D conc. <50 nmol/L) were more than twice as likely to have all-cause dementia/AD than those with a concentration ≥ 50 nmol/L after adjustment for age, race, sex, body mass index and education [26]. Similarly, several cross-sectional studies from Europe [33,34] and the US [35–37] suggest a link between low vitamin D status and poor global cognitive function. The risk of cognitive impairment was up to four times greater in severely deficient individuals (25(OH)D conc. <25 nmol/L) compared to the highest quartile with serum concentrations of ≥ 75 nmol/L [36]. It should be noted however that methodological differences often make individual studies difficult to compare, for example varying cut-points used to define vitamin D concentrations, and different assay methods such as radioimmunoassay (RIA) and liquid chromatography tandem mass spectrometry (LC–MS/MS). Standardized laboratory methods and assays would therefore help to ensure comparability of 25(OH)D concentrations [38,39]. Similarly cognitive function is often assessed using different neuropsychological tests, and dementia diagnosed according to different criteria.

One limitation of cross-sectional and case-control studies is that such associations could be a result of disease progression rather than being causal [40]. It is possible that associations could be driven by dietary changes [41] or reduced mobility and outdoor activity associated with disease progression, thus reducing 25(OH)D concentrations due to insufficient sunlight [42,43]. Two trials have assessed the treatment effect of vitamin D on cognitive function with mixed results, though they were compromised by small sample sizes [44,45] and/or the use of very low doses of vitamin D in combination with other nutrients [44]. Two recent, large, prospective studies suggest a temporal relationship between low baseline vitamin D status and subsequent cognitive decline. In elderly Italian adults, severely deficient individuals (25(OH)D conc. <25 nmol/L measured using Diasorin RIA) had a 60 % increased relative risk of substantial cognitive decline over a 6-year period (95 % CI 1.19-2.00) compared with those sufficient (≥ 75 nmol/L) [46]. Similarly, for elderly US men followed for a mean of 4.6 years, those in the lowest 25(OH)D quartile (25(OH)D conc. ≤ 49.7 nmol/L as measured by LC–MS/MS) had borderline increased odds of cognitive decline (OR 1.41, 95 % CI 0.89–2.23) compared with those in the highest quartile (≥ 74.4 nmol/L) [47].

Conclusions

Observational studies suggest an association between low vitamin D concentrations and cognitive impairment and dementia. However cross-sectional studies can only reveal associations, not prove causality. Many of the studies are also difficult to compare due to heterogeneous methodologies, varying cut-points defining vitamin D status and criteria for dementia or cognitive decline. Reverse causation is a particular concern in cross-sectional and case-control studies of vitamin D status and dementia, where disease progression may lead to reduced vitamin D concentrations. Further large prospective studies and randomized controlled trials are therefore needed to clarify the temporal and causal relationships between vitamin D status and dementia. Prospective studies including neuroimaging that are statistically adjusted for potential confounders such as baseline cognitive and physical function are needed to distinguish between underlying cerebrovascular and neurodegenerative mechanisms. Prospective studies will also refine the design and reduce the cost of subsequent trials, which if appropriately designed will determine whether vitamin D supplementation can be used as a cost-effective strategy to prevent or treat dementia.

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Questions and answers

M Curti, Switzerland

Have there been attempts to compare cognitive function in elderly people from countries where nutrition is fortified with vitamin D and those where it is not fortified?

D Llewellyn

Yes, cross-national direct comparisons for cognitive function are very tricky technically. We have data from NHANES in the US where levels of fortification are very different from what we see in the UK or in Italy. The region studied in Italy is very rural where fortification levels are very low. There is data suggesting that dietary intake is linked with cognition in older adults which is surprising as levels were relatively modest, from a study published by a French group in 2011.

E Schleicher, Germany

I wonder if vitamin D crosses the blood-brain barrier?

D Llewellyn

Yes, it does but we do not have any large studies looking at the concentrations in CSF in relation to clinical diagnosis. There have been some small exploratory studies suggesting a link with diagnosis rather than just its presence.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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